C the following amino acid sequence ~~and biological equivalents~~

C ~~thereof possessing a high degree of homology therewith and~~ possessing monocyte chemoattractant activity:

Gln Pro Asp Ala Ile Asn Ala Pro Val Thr Cys Cys Tyr Asn Phe

Thr Asn Arg Lys Ile Ser Val Gln Arg Leu Ala Ser Tyr Arg Arg

Ile Thr Ser Ser Lys Cys Pro Lys Glu Ala Val Ile Phe Lys Thr

Ile Val Ala Lys Glu Ile Cys Ala Asp Pro Lys Gln

wherein,

Met is methionine,	Gly is glycine,
Lys is lysine,	Asp is aspartic acid,
Val is valine,	Asn is asparagine,
Ala is alanine,	Tyr is tyrosine,
Leu is leucine,	Glu is glutamic acid,
Cys is cysteine,	Trp is tryptophan,
Ile is isoleucine,	His is histidine,
Thr is threonine,	Pro is proline,
Phe is phenylalanine, and	Gln is glutamine.

B2 cont

B3 Claim 14. The vector of claim 13, which is [lambda ZAP II] LAMBDA ZAP II.

B4 Claim 17. [A] An *E. Coli* microorganism containing the vector of claim 14.

R E M A R K S

Upon entry of the present amendment, claims 1-7 and 9-25 will be pending in the above-identified application with claims 9-19 standing ready for action on the merits and claims 1-7 and 20-25 being withdrawn from consideration, due to an earlier restriction

requirement made by the Examiner.

The above amendments to the specification and claims do not incorporate new matter into the application. In this regard, the specification has been amended to recite that "LAMBDA ZAP II" is a registered Trademark, and in order to provide generic terminology relating thereto. The amendment to page 8 finds clear support in the accompanying photocopy of certain pages from the Stratagene 1991 Product Catalogue, which is attached hereto as an Appendix. In this regard, please see pages 6, 12 and 13 of the Stratagene Catalogue which are contained in the accompanying Appendix.

The Examiner has required restriction to one of five separate inventions under 35 U.S.C. 121. As indicated in the Examiner's Office Action on page 4, the applicants have provisionally elected with traverse to prosecute the invention of Group V, claims 8-19. Affirmation of this election with traverse is made herein, in order to be fully responsive to the previous restriction requirement. Nonetheless, the applicants reserve the right to file divisional applications on restricted claims 1-7 and 20-25, without prejudice.

In the outstanding Office Action, the Examiner indicated that the Trademark name "LAMBDA ZAP II" should be capitalized wherever it occurs in the specification and be accompanied by generic terminology. The specification has been amended accordingly herein.

Claims 9-19 were rejected under 35 U.S.C. 112, first paragraph and under 35 U.S.C. 112, second paragraph. These rejections of the

claims are respectfully traversed, and reconsideration and withdrawal thereof are respectfully requested based upon the following considerations:

Claim 9 has been amended so that the term "a bioequivalent thereof" is now amended to recite:

> "a bioequivalent thereof which possesses a high degree of homology therewith [i.e., with a nucleotide sequence] and which is capable of encoding a polypeptide possessing monocyte chemoattractant activity".

Based upon the above recitation in claim 9, it is submitted that claim 9 is clearly patentable under 35 U.S.C. 112, first and second paragraphs. It is noted that support for the amendment of claim 9 occurs in the specification at pages 3-4, 6, and 10-11.

Similarly, claim 11 has been amended to recite that "a biological equivalent" of the amino acid sequence provided is:

> "a biologically equivalent thereof, possessing a high degree of homology therewith [i.e., with the amino acid sequence] and possessing monocyte chemoattractant activity".

The amendment to claim 11 finds clear support in the application at pages 5-6, and 10-11.

Regarding the use of the term "a mutation or variation" in claim 10, it is noted that claim 10 has been amended to recite :

> "the bioequivalent contains a mutation or variation in the nucleotide sequence recited [i.e., in claim 9]".

Based upon the amendment made to claim 10, and the fact that claim 10 is dependent upon amended claim 9, it is submitted that claim 10 is patentable under 35 U.S.C. 112, first and second

paragraphs.

Claim 17 was previously rejected based upon the Examiner's contention that LAMBDA ZAP II® vector would function only in *E. Coli* host cells. Claim 17 has been amended to recite that the host cell is an *E. Coli*.

Claim 18 and 19 were rejected by the Examiner for the use of the terms "under conditions that allow for expression". This language still occurs in claims 18 and 19, since it is applicants' contention that these claims are clearly patentable under 35 U.S.C. 112, first and second paragraphs, without amendment of this language.

In support of the above contention, it is submitted to the Examiner that the applicants' claims 18 and 19 may not be deemed unpatentable merely because they utilize functional language, In re Miller, 441 F2d 689 169 USPQ 597 (CCPA 1971); similarly, these claims cannot be adjudged indefinite through their use of functional language at the point of novelty, Ex parte Roggenburk, 172 USPQ 82 (Pat. Off. Bd. App. 1970). Furthermore, objections as to indefiniteness which might otherwise have been properly applied to a product claim have much less force when applied to process claims, like claims 18 and 19, for the production of these products, Ex parte Peter, 59 USPQ 107 (Pat. Off. Bd. App. 1943). This is due to the fact that the functional language occurring in claims 18 and 19 by definition would not read upon non-operative embodiments. For example, applicants' claims 18 and 19 do not read

upon processes which do not allow for culturing of the microorganisms recited in claims 16 or 17.

Based upon each of the above considerations, it is submitted that the outstanding rejections of claims under 35 U.S.C. 112, first and second paragraphs, must be withdrawn.

The Examiner rejected claims 9-19 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Ramb et al. Additionally, claims 9-19 were rejected under 35 U.S.C. 102(a) as anticipated or, in the alternative, under 35 U.S.C. 103 as obvious over Valente et al. Claims 9-19 were also rejected under 35 U.S.C. 103 as being unpatentable over Yoshimura et al. These rejections of the claims are respectfully traversed and reconsideration and withdrawal thereof are respectfully requested based upon the following considerations.

First, the Yoshimura et al reference cited by the Examiner is a disclosure by the present inventors made within one year of their filing date for application (CIP filing date of March 30, 1989). As such, the Yoshimura et al reference is not applicable as prior art under 35 U.S.C. 103 to applicants' claims 9-19. It is noted that applicants are currently in the process of preparing a Declaration in accordance with the holding of In re Katz, 687 F2d 450, 215 USPQ 14 (CCPA 1982), and the same Declaration will be forwarded to the Examiner once received by the undersigned.

Regarding the references of Ramb et al and Valente et al, the Examiner bases ~~his~~ her rejections on a belief that since each reference

discloses a protein possessing monocyte chemotactic activity, one skilled in the art could easily "identify the sequence of an isolated protein". However, as will be discussed further hereinbelow, the prior art does not describe an "isolated protein" and therefore one skilled in the art would not be able to sequence the protein encoded by the cDNA of the present invention even if it was present, albeit in a unique form, in the materials described in the prior art. In this regard, it is submitted to the Examiner that since neither reference discloses the isolated proteins of the present invention, it is impossible for these references to anticipate or make obvious the present inventions being claimed. Even if the prior art described the isolated protein of the present invention, the Examiner has not described a detailed cloning strategy which could be employed to clone and sequence the cDNA of the present invention.

It is submitted to the Examiner that biological fluids often contain many different chemotactic attractants, such as small peptides, different proteins and even non-protein molecules such as leukotrines. Moreover, in some cases such attractants may be small lipids or peptides bound to a protein. Thus, simply because two different materials from biological fluids possess macrophage chemotactic activity, this does not by itself provide a basis to conclude that such materials are identical or obvious over each other under 35 U.S.C. 102 or 35 U.S.C. 103, respectively; or that cDNA constructs for the production of such different materials

would be identical or obvious over each other under the same statutes.

For example, regarding the Ramb et al cited reference, the Abstract thereof simply states that at 27 hours of culture "most activity was found between 10-20,000 (atomic molecular weight)". Likewise, the results obtained after HPLC gel filtration as shown in Figure 4 of the Ramb et al reference, clearly show that chemotactic activity existed in every fraction (but one) of the Ramb et al product for molecular weight fractions of 20-30,000. In this regard, the authors of the Ramb et al reference even state at page 328 thereof, that "multiple molecular weight species could be identified" in the HPLC fractions. Uncertainty with respect to the products analyzed by Ramb et al also is made evident by their statement at page 328 that "it was obvious that the molecular sieve column was not only separating for size but also for other molecular properties as can be seen from the fact that activities are still eluting after the marker vitamin B_{12}".

In other words, the Ramb et al authors are indicating that macromolecules were binding to the sieve column and eluting later than the marker position based on size alone, and that therefore no molecular mass estimate could be reliably assigned to any fraction. Moreover, it is noted that the isoelectric focusing performed by Ramb et al showed a remarkable high degree of heterogeneity existed within their product as may be seen upon review of Figure 2 thereof.

Based upon the above considerations, it should be clear that the chemotactic activity observed by Ramb et al was apparently accounted for by many molecules of different molecular mass and isoelectric points, and not by one molecular entity which could be subsequently defined with any precision. As such, the Ramb et al reference may never anticipate or make obvious applicants' inventions as set forth in claims 9-19, since it is clear that the authors thereof never isolated and identified a polypeptide encompassed by claim 11, which can be encoded by a nucleotide sequence recited in claim 9.

Regarding the cited Valente et al reference, it is reported therein that the purified protein monocyte chemotactic activity had an estimated molecular mass of 14,000. This is different from the peptides produced with the applicants' invention, which possess an estimated molecular mass of about 8,400 Daltons (See pages 4-5 of applicants' specification). As such, since the Valente et al reference does not report the sequence of the polypeptide produced therein, and moreover discloses a polypeptide possessing a molecular weight much higher than applicants', the same can never anticipate or make obvious applicants' claimed inventions.

Further to the above, it is submitted that the above difference in recited molecular weights for the applicants' protein and the Valente protein is not contradictory with the disclosure of Yoshimura et al and FEBS, Volume 24, No. 2, pages 487-493 (a reference already of record), which states that the Valente protein

and applicants' protein have identical amino acid compositions. This is true, since amino acid compositions are always reported as a relative number (i.e., a percentage or a ratio) whereas molecular weights are always reported as an absolute number (i.e., atomic molecular weights or Daltons).

Based upon the above considerations, the Examiner is respectfully requested to withdraw all outstanding rejections of applicants' claims under 35 U.S.C. 102 or 35 U.S.C. 103 over the references cited because the prior art does not teach, suggest or render obvious the cDNA of the present invention.

STATEMENT UNDER MPEP 2001.06(b)

In order to fully comply with applicants' duty of disclosure as set forth under 37 C.F.R. 1.56(a), the Examiner's attention is directed to the existence of the following copending U.S. patent applications, relating to subject matter which may be material to the examination of the above-identified application.

The confidential status of the following applications as set forth under the provisions of 35 U.S.C. 122 is not waived by the present disclosure.

Serial Number	Filing Date
07/698,183	May 6, 1991 ABN
07/459,245	December 29, 1989 ABN
07/686,264	November 18, 1991 on appeal

Should the Examiner have any questions concerning the

amendments or remarks made herein, she is respectfully requested to contact Mr. John W. Bailey (Reg. No. 32,881) in the Washington Metropolitan Area at 703/241-1300.

Similarly, should the Examiner deem that the present amendments do not place claims 9-19 into form for allowance, she is respectfully requested to contact Mr. John W. Bailey at the above address, in order that a personal interview might be scheduled. In such an interview, Mr. Bailey would be accompanied by one or more of the named inventors of the present application. It is submitted to the Examiner that if the present amendment does not place claims 9-19 into form for allowance, then such a personal interview would be warranted, in order to further the claims towards allowability.

Pursuant to 37 C.F.R. 1.17 and 1.136(a), the Applicants respectfully request a three (3) months extension of time for filing a response in connection with the present application and the required fee of $730.00 is attached hereto.

Please charge any fees or credit any overpayment pursuant to 37 C.F.R. 1.16 or 1.17 to Deposit Account Number 02-2448.

Respectfully submitted,

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Enclosure - Appendix